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* NOTICES *

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[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention is in the living body, and it relates to the calcium phosphate system drug gradual release object which can control the emission rate of a drug, and its manufacture approach while relating to the calcium phosphate system drug gradual release object which continues at a long period of time and is emitted continuously, and its manufacture approach, joining and making it maintain a hard-tissue medical-application drug firmly to the inside of the living body hard tissue especially.
[0002]
[Background of the Invention] From the former, the drug gradual release object has been used as an effective means for continuous prolonged medication against the affected part. And it comes to consist of this drug gradual release object a predetermined drug and a base material holding it, and it is laid underground into hard tissue, such as a bone in the living body, it continues at a long period of time, makes a drug emit gradually, and raises an effective curative effect from a base material to the affected part as known well.
[0003] So, as this drug gradual release object, it is rich in the maintenance capacity of a drug, and the thing excellent in the sustained-release effectiveness is demanded, and in order to satisfy such a demand, it succeeds in various proposals from the former.
[0004] For example, after clarifying the drug solution sinking-in porous ceramics which made the predetermined drug sink in at JP,59-101145,A into the pore which is outside open for free passage and mixing with ceramic impalpable powder and drugs powder at JP,3-161429,A, what carried out pressing in ordinary temperature is indicated, a hole is further made in a substantia-compacta ceramic object in JP,3-294221,A, and the thing which made the liposome which contained the drug inside form in this hole is proposed. And if it is in these official reports, it is shown that the drug gradual release object indicated there is excellent in sustained-release [of a drug], all continues at a long period of time, and reactions of medication are obtained.
[0005] However, since each of those drug gradual release objects was things you are made to come to fabricate by the predetermined form, they needed to process the configuration adapted to the part laid underground into the precision, and the processing was very troublesome [objects] so that it might face laying such a drug gradual release object underground in the living body hard tissue of a complicated configuration and might not drop out of the inside of this living body hard tissue.
[0006] And like the above-mentioned, in in the living body, the chisel configuration of

them is carried out so that a drug may be made to emit in the long run. so, an application site in the living body, the class of illness, etc. -- responding -- comparatively -- a short period of time -- or so that it may continue more at a long period of time and a drug may be made to emit It was that in which it is inherent to make the emission rate of a drug control alternatively and to obtain more effective reactions of medication also in the problem of being difficult.

[0007]

[Problem(s) to be Solved] The place which succeeds in this invention in view of the situation like ****, and is made into the solution technical problem in here The place which is to offer the drug gradual release object you join and may be made to maintain more firmly, without requiring time and effort, such as processing, to the inside of the living body hard tissue of a complicated configuration, and is made into another technical problem The emission rate of a drug is made to control easily and it is in offering the manufacture technique of a drug gradual release object according to an application site in the living body, the class of illness, etc. in which the more effective sustained-release effectiveness can be acquired.

[0008]

[Means for Solution] And in order to solve this technical problem, this invention makes the summary the calcium phosphate system drug gradual release object using the self-hardenability calcium phosphate system cement constituent which blends and becomes so that a calcium/P mole ratio may serve as a hydroxyapatite presentation in phosphoric-acid 4 calcium, calcium hydrogenphosphate, or its dihydrate as a base material holding a drug.

[0009] Moreover, this invention so that a calcium/P mole ratio may serve as a hydroxyapatite presentation in phosphoric-acid 4 calcium, calcium hydrogenphosphate, or its dihydrate As opposed to the self-hardenability calcium phosphate system cement constituent which it comes to blend Face making a phosphoric-acid water solution add and harden, and forming the base material of a drug gradual release object, and set concentration of this phosphoric-acid water solution to add to 0.1 to 0.3 millimol /l, and the addition is made into 25 - 70 % of the weight. Also let the manufacture approach of the calcium phosphate system drug gradual release object which controls the voidage of the hardening object acquired to 20 - 60%, and controlled the emission rate of the drug held at this hardening object be the summary kneading and by making it harden.

[0010]

[Elements of the Invention] By the way, these principal component constituent is made to come to blend the self-hardenability calcium phosphate system cement constituent used as a base material holding a drug in the calcium phosphate system drug gradual release object according to this invention, so that phosphoric-acid 4 calcium (TeCP), calcium hydrogenphosphate (DCPA), or its dihydrate (DCPD) may be used as the principal component constituent and the calcium/P mole ratio may moreover serve as a hydroxyapatite presentation. That is, in this self-hardenability calcium phosphate system cement constituent, these TeCP(s), DCPA, or DCPD is made to blend in an amount from which a calcium/P mole ratio is set to 1.67, and this constituent will be quickly transferred to a hydroxyapatite crystal after hardening by it.

[0011] In here, hydroxyapatite is excellent in biocompatibility, in in the living body, is incorporated as bony [a part of], or may be absorbed as known well.

[0012] Therefore, in the calcium phosphate system drug gradual release object

concerning this invention, when there is no need of being taken out after the completion of emission of a drug and the deficit section, the opening section, etc. are in a bone, when saved by in the living body, the advantage of playing a role of an alternative bone is acquired rather.

[0013] Moreover, if it is in this calcium phosphate system drug gradual release object, hydroxyapatite powder is made to add as seed crystal for making hardening promote advantageously to the calcium phosphate system cement constituent which has the presentation like the above. In addition, as an addition of this hydroxyapatite powder, it is 60 or less % of the weight preferably.

[0014] And to the calcium phosphate system cement constituent which has a writing **** presentation, kneading of the phosphoric-acid water solution is added and carried out, a further predetermined drug is made to mix or mix, and the calcium phosphate system drug gradual release object according to this invention is constituted so that it may mention later.

[0015] Namely, this calcium phosphate system drug gradual release object To the calcium phosphate system cement constituent which has a special presentation, a phosphoric-acid water solution is made to add and they are kneaded. While making hardening advance, a predetermined drug in the condition of the shape of a slurry or clay in the state of independent powder or granulation or as porosity granulation which made mixed fine particles with the high molecular compound which does not have harmfulness to a living body, or a drug contain It adds, and they are kneaded further and it is obtained. Moreover, such drug powder or drug granulation, Or the Plastic solid which fabricated drugs, such as mixed fine particles with a high molecular compound or drug content porosity granulation, etc. in predetermined configurations, such as a tablet, is acquired. A phosphoric-acid water solution adds and you are made to knead, and even if it covers so that the perimeter of this Plastic solid may be covered with the calcium phosphate system cement constituent made into the shape of clay, it can obtain.

[0016] In addition, if it is when fabricating such a drug etc. in a predetermined configuration and covering it with a calcium phosphate system cement constituent especially, they are able to be gradually prescribed for the patient, respectively, using the drug with which a class differs from concentration two sorts or more than it. That is, while carrying out a laminating so that you may make it the drug with which these classes differ from concentration located in the said alignment, respectively and the whole front face of an inside layer may be covered with an outside layer It is made to be made for a drug to be eluted one by one from layers, such as a drug [directly under] of an enveloping layer which consists of this cement constituent, by covering the outermost layer with this calcium phosphate system cement constituent, and constituting a calcium phosphate system drug gradual release object. Generally in here, the medical-application drug of hard tissue, such as bone growth tropic hormones, an antibiotic, an antiinflammatory drug, and an anticancer agent, etc. will be used as a drug contained on this drug gradual release object.

[0017] And if it is in the calcium phosphate system drug gradual release object acquired in this way It fills up in the hard tissue of living bodies, such as the bony deficit section, in the slurry before hardening of a self-hardenability calcium phosphate system cement constituent is completed, or a clay-like condition. any -- although -- by it Without requiring troublesome processing etc. entirely, it is based on the complicated

configuration in the living body hard tissue, and may be laid underground. By completion of hardening further Stable reactions of medication may be secured without being joined more firmly and dropping out of the inside of this living body hard tissue to this living body hard-tissue part laid underground.

[0018] Moreover, although a calcium phosphate system cement constituent is strong acid nature, since it reaches near neutrality (pH 7.0-7.4) immediately by adding and kneading a phosphoric-acid water solution, this drug gradual release object is presenting abbreviation neutrality, therefore there is little living body stimulative and the stability of an addition drug may be secured advantageously.

[0019] By the way, a phosphoric-acid water solution is made to add and harden to the **** self-hardenability calcium phosphate system cement constituent which manufactures such a calcium phosphate system drug gradual release object upwards, and was especially described above if it was in this invention, and it faces forming the base material holding a drug, and this phosphoric-acid water solution is the concentration of 0.1 - 0.3 millimol / l, and it is made to add with 25 - 70% of the weight of an addition. If it is **, and it is because phosphoric-acid concentration will be too low and hydration hardening of a calcium phosphate system cement constituent will not advance, if the concentration of a phosphoric-acid water solution is lower than 0.1 millimols / l and is higher than 0.3 millimols / l Are because acidity will be too high, this cement constituent will dissolve and stimulative [to a living body] will be raised, and further, if there are few the additions than 25 % of the weight If there are too few additions of a phosphoric-acid water solution, and sufficient hardening reaction does not advance but a phosphoric-acid water solution is made to add further again exceeding 70 % of the weight It is because the rate of dissolution of about [that the degree of hardness of the hardened material obtained is inadequate] and drugs becomes quick too much and the effective sustained-release effectiveness is no longer acquired.

[0020] And although the calcium phosphate system cement constituent the phosphoric-acid water solution was made to add is made to harden by carrying out kneading in this way, in this invention, the voidage of the hardening object acquired by that cause is controlled to 20 - 60%. If it is when a hardening object carries out eburnation, and there is a possibility that emission of the drug which leads the opening of this hardening object may be checked and it exceeds 60%, if it is when this voidage is less than 20%, the maintenance capacity of a drug declines and there is a problem on which that sustained-release effectiveness decreases remarkably.

[0021] That is, if it is in the calcium phosphate system drug gradual release object manufactured according to this invention in this way, while the self-hardenability calcium phosphate system cement constituent used as a base material holding a drug has a predetermined opening after the hardening and a drug is made to emit through the opening, the emission rate of the drug held is greatly dependent on the voidage.

[0022] Moreover, if it is in this invention, it is possible to control the voidage of the hardened material of the self-hardenability calcium phosphate system cement constituent obtained by changing suitably into within the limits like the above the concentration and the addition of a phosphoric-acid water solution you are made to add to a calcium phosphate system cement constituent.

[0023] So, in this this invention, the concentration and the addition of a phosphoric-acid water solution you are made to add are only controlled, and it may succeed in control of

the emission rate of the drug held at the hardening object of a calcium phosphate system cement constituent very simply.
[0024] Therefore, according to such this invention, the calcium phosphate system drug gradual release object according to the part where it is applied in the living body, the class of illness, etc. which can enjoy the more effective sustained-release effectiveness will be acquired very easily.
[0025] In addition, in this invention, also by adjusting the particle diameter of TeCP which constitutes a self-hardenability calcium phosphate system cement constituent, or DCPA or DCPD, the voidage of the hardening object acquired can be changed and the drug release rate from a hardening object can be controlled by it still more extensively. Furthermore, by using the granulation which coated with various poly membranes the front face of the drug powder with which particle diameter differs in the drug you are made to mix or mix, or a drug, controlling the rate of dissolution of a drug also controls the drug release rate from a hardening object upwards, and it is effective again.
[0026]
[Example] It is a place needless to say that this invention is not what also receives any constraint by the publication of such an example although some examples of this invention are shown below and this invention is clarified still more concretely. Moreover, it should be understood that it is what can add modification which becomes various, correction, amelioration, etc. to this invention based on this contractor's knowledge unless it deviates with the meaning of this invention besides the following examples besides the further above-mentioned concrete description.
[0027] example 1 -- first, weighing capacity of the 0.86g of the 1.794g of the synthetic hydroxyapatite (HAp) powder was further carried out [phosphoric-acid 4 calcium (TeCP) powder] for 1.83g and calcium hydrogenphosphate dihydrate (DCPD) powder, respectively, and the mixing powder which mixes them and gives a self-hardenability calcium phosphate system cement constituent was obtained. Subsequently, it kneaded quickly and the cement slurry was prepared, after carrying out 0.95g weighing capacity of this mixed powder and adding 0.36ml of phosphoric-acid water solutions of 0.25 millimols / l to this. then -- this -- obtaining -- having had -- cement -- a slurry -- 0.05 -- g -- indomethacin -- powder -- adding -- having kneaded -- after -- a diameter -- two -- cm -- a mold -- slushing -- in the living body -- abbreviation -- the same -- conditions -- becoming -- temperature -- 37 -- degree C -- relative humidity -- 100 -- % -- 24 -- an hour -- holding -- this -- hardening -- making -- indomethacin -- content -- calcium phosphate -- a system -- a drug -- gradual release -- the body -- it is -- a sample -- one -- having obtained .
[0028] And the X-ray powder diffraction (CuKalpha, 30kv, 15mA) was performed with Composition HAp about the sample 1 obtained in this way, respectively. Each X-ray powder diffraction diagram is shown in drawing 1 and drawing 2 .
[0029] Composition HAp and a sample 1 show the same peak location, a sample 1 has the same crystal structure as Composition HAp, the peak intensity of a sample 1 is low to the peak intensity of Composition HAp, and the sample 1 has brought a result it is indicated to be that it is what has the structure near HAp with a little low degree of crystallinity which constitutes a living body more from Composition HAp so that clearly from these drawing 1 and drawing 2 .
[0030] Next, in order to investigate the emission rate of the drug of the calcium

phosphate system drug gradual release object which are obtained by carrying out like the above, in the sample 1, the elution volume (burst size) of the indomethacin for every fixed time amount was measured. The measurement result is extracted and is shown in Table 1. In addition, on the occasion of measurement of the elution volume of the indomethacin from this sample 1, the rotating-disc method was adopted and it carried out by [as being the following] using the elution test machine of the 11th amendment Japanese pharmacopoeia. First, making only one field of a sample 1 expose, the whole was hardened with the wax and sample braces were equipped. Subsequently, said elution test machine is used, 50ml of phosphate buffer solutions of pH7.4 is put into a 1000ml round bottom flask, and it is 150rpm about a sample 1 at the temperature of 37 degrees C. You made it rotate and made it indomethacin eluted. Extraction of the indomethacin you were made to be eluted was performed for every fixed time amount, and exchanged the whole quantity of a solvent each time. And the amount of the extracted indomethacin was measured on the wavelength of 264nm using the spectrophotometer.

[0031]

[Table 1]

[0032] In the sample 1, indomethacin carries out abbreviation whole-quantity elution over about two weeks, it continues at about two weeks, and reactions of medication are obtained and this calcium phosphate system drug gradual release object has brought a result it is indicated to be that the outstanding sustained-release effectiveness is demonstrated so that clearly also from this table 1.

[0033] Example After adding 0.36ml of phosphoric-acid water solutions of 0.25 millimols / l to 1.0g of mixed powder of the self-hardenability calcium phosphate system cement constituent obtained like two examples 1, to it, it kneaded quickly and the cement slurry was prepared to it. Slushed into the mold with a diameter of 2cm, 5mg, in addition after kneading, hold insulin powder in the SEMMEN toss rally obtained in this way for 24 hours, and it was made to harden it at conditions in the living body, the temperature of 37 degrees C of abbreviation identitas, and 100% of relative humidity, and the sample 2 which is an insulin content calcium phosphate system drug gradual release object was obtained. And the elution test of an insulin was performed like the example 1 to this sample 2. The result is shown in Table 2. In addition, in the quantum of an insulin, it measured on the wavelength of 595nm with the spectrophotometer using protein measurement kit:Bio-Rad.

[0034]

[Table 2]

[0035] In the sample 2, the insulin is eluted about 28% among about three weeks, the elution of an insulin can be expected also in next, this calcium phosphate system drug gradual release object is further rich in insulin maintenance capacity much more, and it is shown that the more excellent sustained-release effectiveness is acquired so that clearly also from this table 2.
[0036] Example The mixed powder of the various calcium phosphate system cement constituents with which weighing capacity of TeCP powder and the DCPD powder is carried out, weighing capacity of the composition HAp is carried out so that it may become the **** blending ratio of coal further shown in the following table 3 to these, they are mixed, respectively and the contents of Composition HAp differ like three examples 1 was obtained. Subsequently, after adding the phosphoric-acid water solution of 0.25 millimols / l in a various amount, respectively, it kneaded quickly and various cement slurries were prepared, so that it might become a powder-liquid ratio like the following table 3 to each mixed powder obtained in this way. Then, respectively slushed this obtained cement slurry into the mold with a diameter of 13mm, held it for 24 hours with the temperature of 37 degrees C and 100% of relative humidity which is in the living body and abbreviation same conditions, this was made to harden, and various calcium phosphate system cement was obtained.
[0037] On the other hand, aspirin powder and 50% of synthetic HAp powder were mixed, it pressurized by the pressure of 2t to the obtained mixed powder, and the tablet with a diameter of 13mm which consists of these aspirin and 50% of composition HAp was fabricated. And it carried out to this tablet like the above, and the laminating of the calcium phosphate system cement made to harden was carried out, and it considered as the two-layer lock, and further, while hardening with the wax so that a front face might be respectively covered for these two-layer lock, only the front face of calcium phosphate system cement was made to expose, and the samples 3-8 which are aspirin content calcium phosphate system drug gradual release objects were obtained, respectively.
[0038] And it asked for each voidage in the samples 3-8 obtained by doing in this way. The result is collectively shown in the next table 3.
[0039]
[Table 3]

[0040] It is admitted that the voidage of the hardening object acquired increases and it has brought a result shown that the voidage of the hardening object acquired by this is dependent on the addition of a phosphoric-acid water solution as the addition of the phosphoric-acid water solution of 0.25 millimols / l is made for concentration to increase to a calcium phosphate system cement constituent, so that clearly also from this table 3.
[0041] Next, in order to investigate each drug release rate in these samples 3-8, the elution test of aspirin was performed. What expressed the result of this trial with the graph was shown in drawing 3 . In addition, it carries out by adopting a quiescence disk method, and you make it samples 3-8 immersed, respectively into 50ml of 0.1-mol phosphate buffer solutions which are pH7.4 and were held at the temperature of 37 degrees C, it sets in this solution, and this elution test is 200rpm about a magnetic stirrer. You stirred this solution and made it aspirin eluted by making it rotate. Moreover, extraction of the aspirin you were made to be eluted was performed for every fixed time amount, and exchanged the whole quantity of a solution each time.
[0042] With the increment in voidage, the rate of dissolution of aspirin is increasing and that the emission rate of aspirin is controlled easily has brought a result shown by making by this the addition of the phosphoric-acid water solution you are made to add by the calcium phosphate system cement constituent fluctuate in the aspirin content calcium phosphate system drug gradual release object of this example so that clearly also from this drawing 3 . In addition, when X-ray powder diffraction was performed to samples 3-8, respectively, the transition to hydroxyapatite excellent in biocompatibility was checked from those X-ray powder diffraction diagrams.
[0043]
[Effect of the Invention] If it is in the calcium phosphate system drug gradual release object according to this invention so that clearly from the above explanation As a base material holding a drug, from using the self-hardenability calcium phosphate system cement constituent which consists of phosphoric-acid 4 calcium which has a predetermined presentation ratio, calcium hydrogenphosphate, or its dihydrate, respectively By filling up in a living body's hard tissue in the slurry before hardening is completed, or a clay-like condition Carry out self-hardening in the configuration adapted to this hard tissue, and, so, it faces laying underground in the living body hard tissue like the conventional drug gradual release object. Without completely losing the need of

processing it into a precision in the configuration adapted to the part laid underground, and taking the time and effort of such processing in any way, in the living body hard tissue of a complicated configuration, you will join, it may be made to maintain firmly, and more stable reactions of medication may be secured.
[0044] Moreover, only by changing suitably the concentration and the addition of a phosphoric-acid water solution you are made to add in order to harden this calcium phosphate system cement constituent within the limits of predetermined according to this invention technique The voidage of the hardening object acquired can be controlled very easily. Moreover, by it It will be obtained very easily [the emission rate of the drug held at this hardening object may be controlled efficiently, with / the calcium phosphate system drug gradual release object according to the part in the living body where it is applied, the class of illness, etc. which can enjoy the more effective sustained-release effectiveness].

[Claim(s)]
[Claim 1] The calcium phosphate system drug gradual release object characterized by using the self-hardenability calcium phosphate system cement constituent which blends and becomes so that a calcium/P mole ratio may serve as a hydroxyapatite presentation in phosphoric-acid 4 calcium, calcium hydrogenphosphate, or its dihydrate as a base material holding a drug.
[Claim 2] Phosphoric-acid 4 calcium, calcium hydrogenphosphate, or its dihydrate so that a calcium/P mole ratio may serve as a hydroxyapatite presentation As opposed to the self-hardenability calcium phosphate system cement constituent which it comes to blend Face making a phosphoric-acid water solution add and harden, and forming the base material of a drug gradual release object, and set concentration of this phosphoric-acid water solution to add to 0.1 to 0.3 millimol /l, and the addition is made into 25 - 70 % of the weight. The manufacture approach of the calcium phosphate system drug gradual release object characterized by controlling the voidage of the hardening object acquired kneading and by making it harden to 20 - 60%, and controlling the emission rate of the drug held at this hardening object.